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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,235	04/18/2001	Christopher P. Marshall	9725-005	1399

7590 07/08/2004

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,235	MARSHALL ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-13,18-20 and 22-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13,18-20 and 22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Non-Final Action

1. Applicants' Amendment After Final filed May 28, 2004 has been entered. Claims 1-9, 14-17 and 21 have been cancelled.

2. Claims 10-13, 18-20 and 22-39 are pending and under consideration in this examination.

3. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

4. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

5. ***Abstract***

*This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.
*The abstract should be in narrative form and generally limited to a single paragraph within the range of 50 to 150 words [in length since the space provided for the abstract on the computer tape by the printer is limited]. The form and legal phraseology often used in patent claims, such as "means" and "said", should be avoided in the abstract. The abstract should sufficiently describe the disclosure to assist readers in deciding whether there is a need for consulting the full patent text for details. MPEP 608.01(b).

THE ABSTRACT IS MORE THAN 150 WORDS.

6. The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (for example, page 108, line 14) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

7. ***Claim Rejections - 35 USC § 112*** (first paragraph)

Claims 10-13 & 22-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated stabilized lipase B of *Candida antartica* 'CALB' and subtilisin E (only specific polypeptides exemplified in the specification), comprising at least one di-tyrosine cross-link, wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation to tyrosine, and wherein the cross-linked protein retains lipase activity (original function), does not reasonably provide enablement for any isolated protein comprising a di-tyrosine cross-link by wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 10-13 & 22-39 are drawn to 'an isolated protein (or composition, kit or method of making stabilized protein) comprising at least one di-tyrosine cross-link', wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation, wherein the protein is a hormone, a receptor, a growth factor, an enzyme or an antibody, or a fragment thereof.

Genetic modification of the protein structure to introduce or substitute an amino acid or a tyrosine is known (example – Brown et al. (1998) [IDS, (AC)]. Cross-linking of tyrosine residues has been achieved by chemical methods and under defined conditions such as in the presence of oxidants : hydrogen-peroxide oxone and monoperoxyphthalic acid (MMPP). However, cross-linking tyrosyl-tyrosyl residues of any protein, wherein the protein retains at least one function would require additional guidance to one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

The specification provides two example for the preparation stabilized lipase B of *Candida antartica* and subtilisin E by introducing at least one tyrosine in the peptide chain by point mutation and cross-linking di-tyrosine within the same polypeptide chain. Lipase B of *Candida antartica* has been selected because there are significant number of aromatic residues available in the sequence of CALB, and because mutation of an aromatic amino acid residue to tyrosine would be maximally conservative. Only residue pairs that are spaced more than 40 amino acids apart in the two-dimensional amino acid sequence are selected. Further, for retention of at least one function, the conditions for using oxidizing agent(s) for individual protein(s) (as encompassed by the claims) will have to be optimized [see Specification pages 108 (last paragraph) and 109, for example). This is because oxidative modifications to a protein occurs most readily to the side chains of the amino acid residues cys, met, trp, tyr, his and phe [see Kanwar et al. Exp. Eye res (1999), 68 : 771-784, Applicants' Information Disclosure Statement, IDS (AK)). Therefore, the cross-linking by oxidation is non-specific and can cross-link other residues in a protein as well, leading to unpredictability in obtaining a stabilized and functional protein. Because of the nature of the art as discussed above, it is be amply clear that it would be beyond the expertise of a skilled artisan, to take guidance from the very narrow, specific and rigid conditions optimized for CALB or subtilisin E [known hardy enzymes which have been widely used in detergent compositions for being stable at high temperature], and apply across the board for introducing and cross-linking di-tyrosine residues in any protein, hormone, antibody, enzyme or fragment thereof. In spite of the fact that these enzymes are considered as hardy enzymes, the specification provide no evidence that the point mutated and cross-linked CALB or subtilisin E [the specific embodiments disclosed] were functionally active. No tests or assays

demonstrating the activity levels of these enzymes before and after the treatment has been shown in the instant specification. This question is raised because of demonstrated effects of oxidizing agents in inactivating enzyme or binding activities. The instability in retaining function during the cross-linking is further demonstrated in the works of Brown et al. (1998), and so well argued by the Applicants [see Applicant response filed may 28, 2004 [reference 023, IFW page 8, IDS - AC], that the 102(b) rejection was withdrawn. As far as fragments (claims 13) are concerned a 2-amino acid residue (or di-tyrosine fragment) cannot retain any functionality of the original protein. Claims to composition, kit or method of making such a protein are similarly not enabled.

No specific examples other than CALB or subtilisin E are outlined in the specification that teach or provide guidance for stabilizing any protein subjected to point mutation and cross-linking tyrosine residues or a method of obtaining such a cross-linked protein, wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation, and wherein the protein is a hormone, a receptor, a growth factor, an enzyme or an antibody.

There is no common strategy that can be employed to all or any protein based upon two examples, viz., CALB and subtilisin B. Every protein species will have to be optimized with respect to introduction of tyrosine by point mutation, conditions for cross-linking [by oxidation] and with respect to stabilization of the desired function.

Without sufficient guidance, determination of any protein from any source having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' Arguments :

Applicants argue that claims 10-13 and 22-26, rejected under 35 USC § 112 is not enabling as per the Examiner "for any isolated protein comprising a di-tyrosine cross-link, wherein at least one tyrosine of a di-tyrosine cross-link originates by point mutation".

In response, it is pointed out that Applicants do have basis for 'point mutation' in their specification. Examiner's objection was to earlier claim language, wherein 'cross-linking' of the tyrosine pair was achieved by point mutation. Since cross-linking of tyrosine residues can be achieved, for example, by chemical means, and cannot be achieved by point mutation, the issue was raised. Applicants have focused their entire arguments on this issue, which as indicated is not the issue any more.

The main issue concerning enablement are that the Applicants are enabled for 2 species - lipase B of *Candida antartica* 'CALB' and subtilisin E not for any protein, antibody, enzyme or fragment thereof.

8. ***35 U.S.C. 112, first paragraph (Written Description) -New***

Claims 10-13 & 22-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 10-13 & 22-39 are drawn to 'an isolated protein (or composition, kit or method of making stabilized protein) comprising at least one di-tyrosine cross-link', wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation, wherein the protein is a hormone, a receptor, a growth factor, an enzyme or an antibody, or a fragment thereof.

The specification, however, only provides two representative species from lipase B of *Candida antartica* 'CALB' and subtilisin E. There is no disclosure of any particular structure to function/activity relationship in the two disclosed species to other species where such molecules (or proteins) can be similarly di-tyrosine cross-linked in order to establish a relationship among species wherein the cross-linking standardized method for the two exemplified species be applicable to the entire genus. The specification also fails to describe additional representative species of these proteins/enzymes by any identifying characteristics other than the mere mention of 'an isolated protein' recited in claims, for which no predictability of function is apparent. Given this lack of additional representative species, such as the numerous proteins with no defined activity or function or name, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

9. Claim Rejections - 35 USC § 112 (second paragraph)

Claims 20 & 35 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 & 35, lines 1-2, recites 'wherein cross-linking is catalyzed by a catalyst selected from the group consisting of polyhistidine, Gly-Gly-His, metalloporphyrin, a peroxidase or any combination thereof'. The claim is indefinite because it is unclear what cross-linking reaction is catalyzed by "polyhistidine, Gly-Gly-His, metalloporphyrin, or a peroxidase". Clarification is required.

Claim 36-39, lines 2, recites 'protein comprises an enzyme, an antibody or a fragment thereof'. The claim is indefinite because 'a protein or chimeric polypeptide comprises amino acids residues' and not an enzyme, an antibody or a fragment thereof. Amending the claim to recite "wherein a protein is an enzyme or an antibody" will overcome this rejection

Claims 37-39 are included in the rejection for failing to correct the defect present in the base claim(s).

10. Claims 18-20 & 30-39 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: (c) cross-linking the residue pair by reacting with an oxidant.

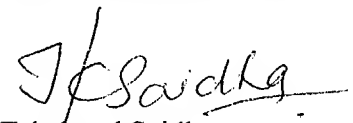
11. No claim is allowed.

12. In view of new arguments and new rejection presented in this Office Action the finality of the last office Action is withdrawn.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (571) 272-0940. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group in the Technology Center is 703 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 571 272-1600.



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